



REC'D PCT/PTO 28 SEP 2003

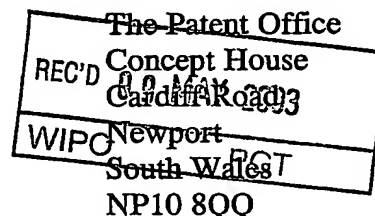
PCT/EP 03 / 03 21

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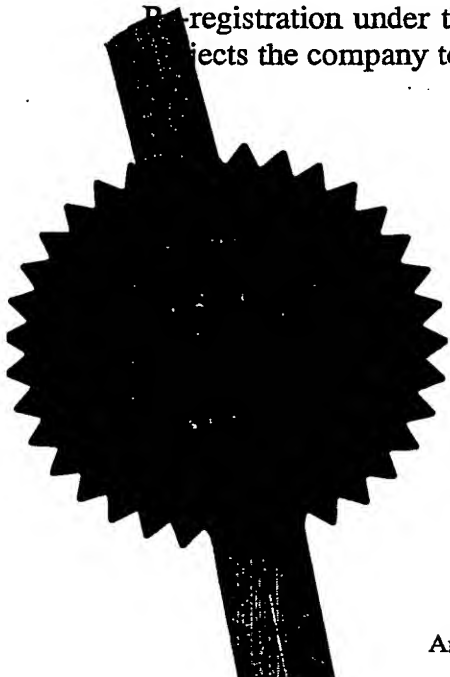


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*R. Mahoney*

Signed

Dated 20 January 2003

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Patents Form 1/77

Patents Act 1977  
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The  
**Patent  
Office**

PCT 03/03215  
30440 07628-1 000524  
P01/7700 0.00-0207495.3

**1/77**

**Request for grant of a patent**

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

28 MAR 2002

The Patent Office

Cardiff Road  
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Gwent NP10 8QQ

1.	Your reference	G-32413P1/BCK 9916		
2.	Patent application number (The Patent Office will fill in this part)	0207495.3		
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	BIOCHEMIE GESELLSCHAFT MBH A-6250 KUNDL/TIROL AUSTRIA 8355158001		
	Patent ADP number (if you know it)			
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA		
4.	Title of invention	Organic compounds		
5.	Name of your agent (if you have one)	B.A. YORKE & CO.		
	"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		
	Patents ADP number (if you know it)	1800001 ✓		
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)	
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. (see note (d))	Yes		

# Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description 23

Claim(s) 3 *DM*

Abstract 1

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

ONE ✓

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11.

I/We request the grant of a patent on the basis of this application

Signature

Date

*B.A. Yorke & Co*

B.A. Yorke & Co.

28 March 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham  
020 8560 5847

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## Notes

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- Once you have filled in the form you must remember to sign and date it.
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## Organic Compounds

The present invention relates to organic compounds, such as compounds which are active in the treatment of diseases caused by *Mycobacterium*.

5    Tuberculosis is a chronic infectious disease caused by infection with *Mycobacterium tuberculosis*. Tuberculosis is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about 8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly manifested as an acute inflammation of the  
10    lungs, resulting in fever and a nonproductive cough. If untreated, serious complications and death typically result. Tuberculosis may be generally controlled by antibiotic therapy, such as by treatment with Isoniazid, see e.g. The Merck Index, 12th edition, item 5203; Rifampin (Rifampicin®), see e.g. The Merck Index, 12th edition, item 8382, Streptomycin, see e.g. e.g. The Merck Index, 12th edition, item 8983; but a major problem is the development of  
15    strain drug resistance against such antibiotics.

We have now found that a compound class which is known to have antibiotic activity shows surprisingly activity in the treatment of diseases caused by *Mycobacterium*, even against  
20    drug resistant strains.

In one aspect the present invention provides the use of a pleuromutilin in the preparation of a medicament for the treatment of diseases caused by *Mycobacterium*.

In another aspect the present invention provides a method of preventing or treating diseases  
25    caused by *Mycobacterium*, comprising administering to a subject in need of such treatment an effective, e.g. an anti-mycobacterium effective; amount of a pleuromutilin.

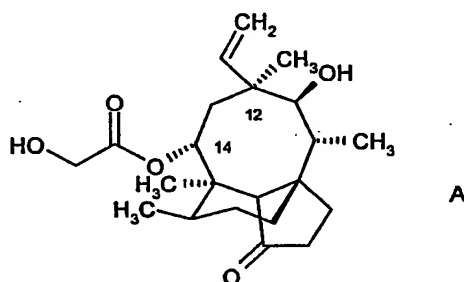
*Mycobacterium* includes *M tuberculosis*. Diseases caused by *Mycobacterium* include mycobacterium infections. A pleuromutilin includes one or more pleuromutilins.

30    A pleuromutilin for use according to the present invention or for treating or preventing diseases according to the present invention is designated hereinafter as "a pleuromutilin of the present invention".

A pleuromutilin of the present invention includes a pleuromutilin in the form of a free base, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate, e.g. and in the form of a complex, such as a cyclodextrin complex.

- 5 A pleuromutilin of the present invention may exist in the form of isomers and mixtures thereof, e.g. including diastereoisomers and mixtures thereof. Isomeric or diastereoisomeric mixtures may be separated as appropriate, e.g. according to a method as conventional, to obtain pure isomers or diastereoisomers, respectively. The present invention includes a pleuromutilin according to the present invention in any isomeric and diastereoisomeric form  
 10 and in any isomeric and diastereoisomeric mixture. Preferably the configuration in the mutilin ring is the same as in a naturally produced mutilin.

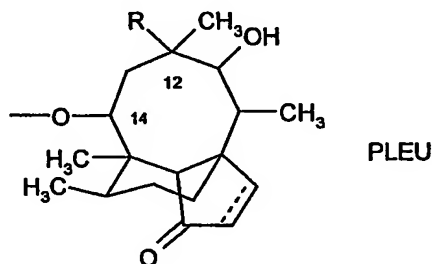
Pleuromutilin, a compound of formula



- 15 is a naturally occurring antibiotic, e.g. produced by the basidiomycetes *Pleurotus mutilus* and *P.passeckerianus*, see e.g. The Merck Index, 12th edition, item 7694.

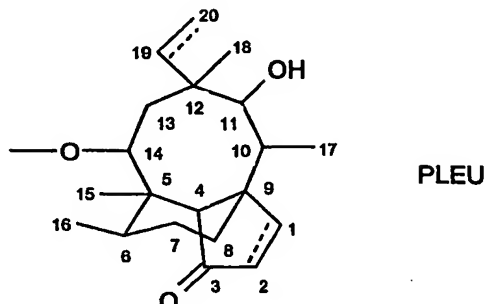
A number of further pleuromutilins having the principle ring structure of pleuromutilin and having e.g. antibacterial activity have been developed.

- 20 A pleuromutilin of the present invention includes a pleuromutilin having the basic structural elements as set out in formula



wherein R is vinyl or ethyl and the dotted line is a bond or is no bond.

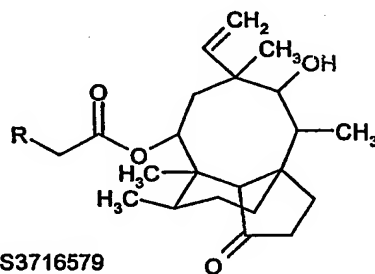
The following numbering system is used in the present application:



The dotted line between positions 19 and 20 (and between positions 1 and 2) is a bond or is no bond. If the dotted line between positions 1 and 2 is no bond the ring system may be further substituted in positions 1 and 2. The group -O- in position 14 is further substituted, preferably by a substituted carbonyl group.

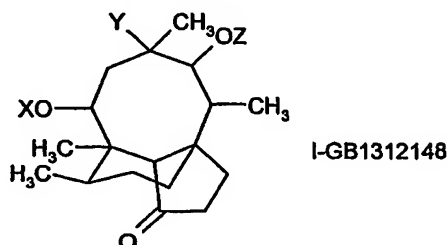
Examples of pleuromutilins according to the present invention includes e.g.

- A compound as disclosed in US3716579, e.g. of formula



wherein R is  $\text{CH}_3-(\text{CH}_2)_7-\text{CH}=\text{CH}-(\text{CH}_2)_7-\text{COO}-$ ,  $\text{CH}_3-(\text{CH}_2)_4-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_7-\text{COO}-$ ,  $\text{CH}_3-(\text{CH}_2)_9-\text{CH}=\text{CH}-(\text{CH}_2)_7-\text{COO}-$  or hydrogen;

- A compound as disclosed in GB1312148, e.g. of formula

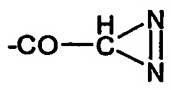


wherein X, Y and Z are as defined in any one of the following groups:

a. X is  $-\text{CO}-\text{CH}_2-\text{R}_1$ , wherein  $\text{R}_1$  is H, Cl, Br, I, thiocyanato, azido, (N,N-tetramethylene-thiocarbamoyl)-mercapto, dithiocarbonic acid-O-( $\text{C}_{1-3}$ )alkyl, -S-phenyl, S-phenyl substituted by carboxyl or by one or two OH, -S-pyridyl, -S-benzyl, -S-( $\text{C}_{1-5}$ )alkyl, or -S-( $\text{C}_{1-5}$ )alkyl substituted by one or more amino, OH or carboxyl, Y is vinyl, and Z is H;

- 4 -

- b. X is CO-CO-OH, Y is vinyl and Z is H;  
 c. X is COCH<sub>3</sub>, Y is vinyl and Z is H;  
 d. X is COCH<sub>2</sub>NH<sub>2</sub>, Y is ethyl and Z is H;  
 e. X is a group of formula

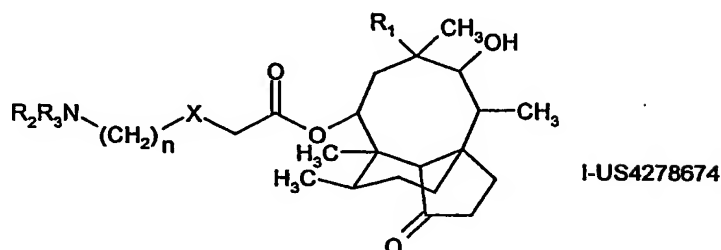


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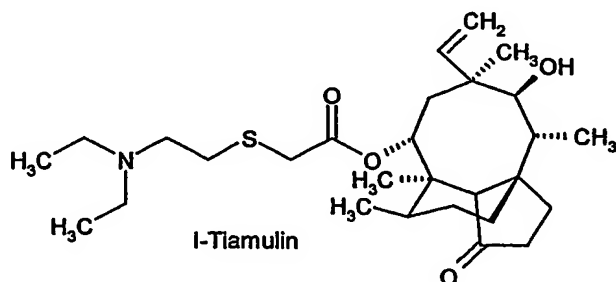
, Y is ethyl and Z is H

- f. X is H, Y is vinyl and Z is acetyl; or  
 g. X is COR<sub>2</sub>, wherein R<sub>2</sub> is (C<sub>1-5</sub>)alkyl, Y is vinyl and Z is H,

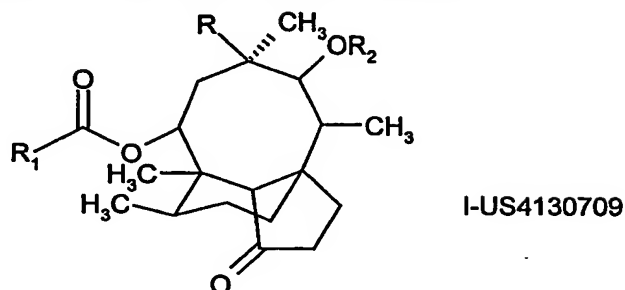
- A compound as disclosed in US4278674, e.g. of formula



- 10 wherein R<sub>1</sub> is vinyl or ethyl, n is an integer from 2 to 5, X is sulphur or a group -Y-  
 phenylene-Z- or a group =NR<sub>4</sub>, Y and Z are both sulphur or one of Y and Z is sulphur and  
 the other is oxygen, R<sub>4</sub> is H or a second mutilin ring of formula US4278674, wherein R<sub>1</sub> is  
 as defined above and attached via a -O-CO-CH<sub>2</sub>- group in position 14; each of R<sub>2</sub> and R<sub>3</sub> is  
 (C<sub>1-10</sub>)alkyl, or R<sub>2</sub> and R<sub>3</sub> together with the nitrogen atom form pyrrolidino, piperidino,  
 15 morpholino, thiomorpholino, or 1-hexahydro-1H-azepino, or R<sub>2</sub> and R<sub>3</sub> together with the  
 nitrogen atom form piperazinyl, the second nitrogen atom of which is substituted by (C<sub>1-5</sub>)  
 alkyl, (C<sub>1-4</sub>)hydroxyalkyl, (C<sub>2-5</sub>)alkynoyloxy(C<sub>1-4</sub>)alkyl, or benzoyloxy(C<sub>1-4</sub>)alkyl, or  
 R<sub>1</sub> is as defined above, n = 2, R<sub>3</sub> is (C<sub>1-10</sub>)alkyl, (C<sub>1-4</sub>)hydroxyalkyl, (C<sub>2-5</sub>)alkynoyloxy-  
 (C<sub>1-4</sub>)alkyl, or benzoyloxy(C<sub>1-4</sub>)alkyl, X is =NR'<sub>4</sub> and R<sub>2</sub> together with R'<sub>4</sub> forms an ethylene  
 20 bridge between both nitrogen atoms; such as  
 - 14-Desoxy-14[(2-diethylaminoethyl)mercaptoacetoxy]mutilin, e.g. also known as tiamulin of  
 formula

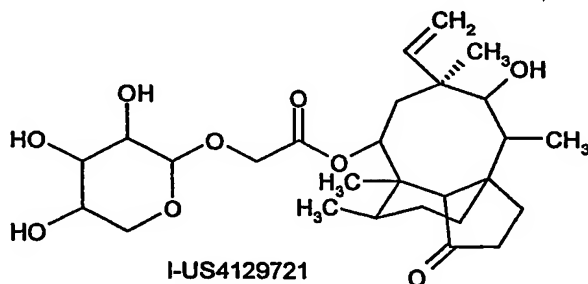


- A compound as disclosed in US4130709, e.g. of formula



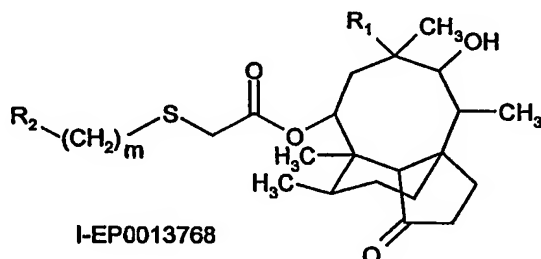
wherein R is ethyl or vinyl, R<sub>1</sub> is selected from α- or β-anomers of hexopyranoses, hexofuranoses, pentopyranoses, pentofuranoses, pyranose and furanose aminosugars, disaccharides, trisaccharides and R<sub>2</sub> is H, benzoyl or (C<sub>2-4</sub>)alkanoyl; or R<sub>1</sub> is 2-deoxy-2-(hydroxyimino)-3,4,6-tri-O-acetyl-α-D-glucopyranosyl or -galactopyranosyl, 2-deoxy-2-(hydroxyimino)-α-D-galactopyranosyl, 2-deoxy-2-amino-4,6-di-O-acetyl-α-D-glucopyranosyl, or 2-deoxy-2-acetamido-3,4,6-tri-O-acetyl-α-D-glucopyranosyl and R<sub>2</sub> is H;

- A compound as disclosed in US4129721; e.g. of formula



and the 19,20-dihydro derivative thereof and the tetra (C<sub>2-6</sub>)alkanoyl derivatives thereof;

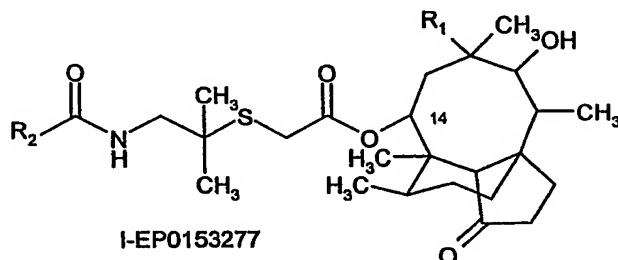
- A compound as disclosed in EP0013768, e.g. of formula



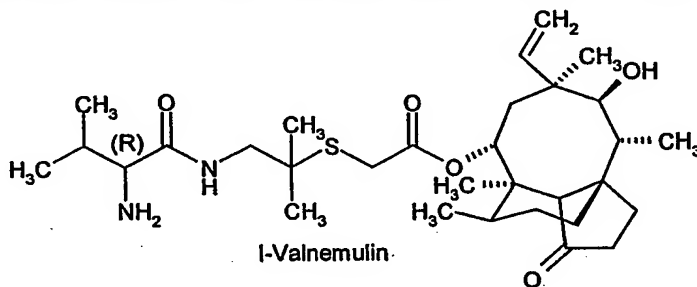
wherein R<sub>1</sub> is vinyl or ethyl, m is 0 or 1, and R<sub>2</sub> is a heterocyclic radical, in which a 5- or 6-membered, unsaturated or saturated heterocyclic ring containing one or more hetero atoms selected from O, S and N, is attached to the -S(CH<sub>2</sub>)<sub>m</sub>- group;



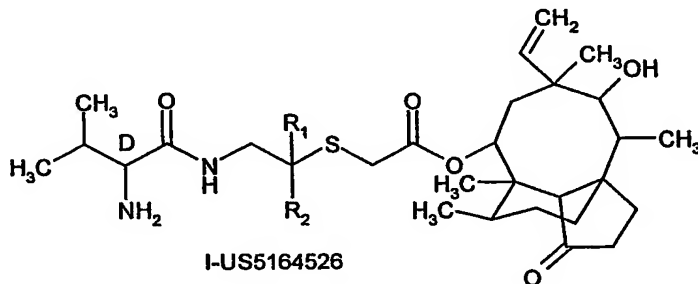
- A compound as disclosed in EP0153277, e.g. an N-acyl-14-O-[(1-amino-2-methylpropan-2-yl)thioacetyl]-mutilin or 19,20-dihydromutionin, such as of formula



wherein  $R_1$  is vinyl or ethyl, and  $R_2$  is optionally hydroxy-substituted aminoalkyl or a 5-membered saturated heterocycle, e.g. including Valnemulin (Econor®) of formula

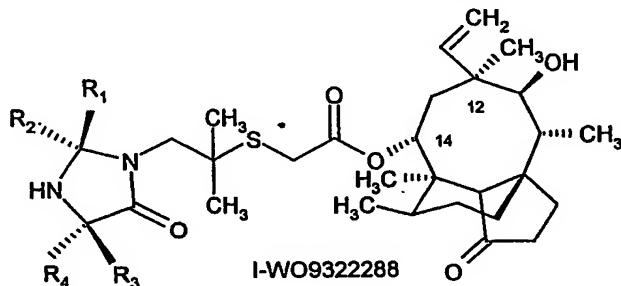


- A compound as disclosed in US516526, e.g. of formula



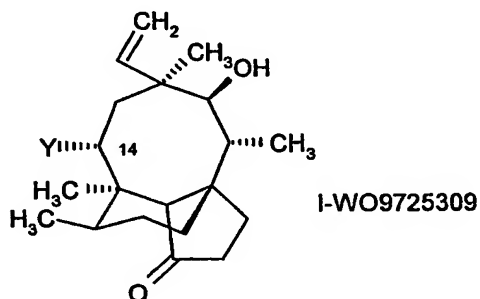
wherein  $R_1$  and  $R_2$  independently of each other are H, alkyl, alkenyl, cycloalkyl, aryl or aralkyl;

- A compound as disclosed in WO9322288, e.g. of formula

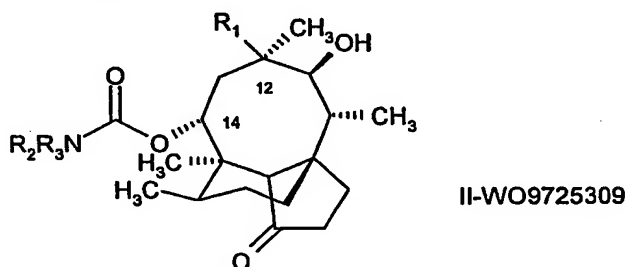


wherein  $R_1$  and  $R_2$  are independently of each other H, alkyl, or,  $R_1$  and  $R_2$  together with the carbon atom to which they are attached are cycloalkyl; and  $R_3$  and  $R_4$  independently of each other are H, alkyl or substituted alkyl;

- A compound as disclosed in WO9725309, e.g. of formula



5 wherein Y is carbamoyloxy, wherein the N-atom is unsubstituted or mono- or disubstituted, such as a compound of formula



10 wherein  $R_1$  is vinyl or ethyl,  $R_2$  and  $R_3$  independently of each other are H, or optionally substituted

- saturated or unsaturated ( $C_{1-6}$ ) hydrocarbon or ( $C_{3-8}$ )cyclic hydrocarbon,
- heterocyclyl or aryl, or

$R_2$  and  $R_3$  together form an optionally substituted cyclic group of 3 to 8 ring atoms, optionally containing one additional heteroatom selected from N, O and S, and optionally fused to a hydrocarbon ring, a heterocyclic group or an aromatic group; or

15  $R_2$  is one of the above monovalent groups and and  $R_3$  is a group selected from  $SO_2R_4$ ,  $COR_5$ ,  $OR_5$  and  $NR_6R_7$ ; wherein

$R_4$  is optionally substituted,

- saturated or unsaturated ( $C_{1-6}$ )hydrocarbon or ( $C_{3-8}$ )cyclic hydrocarbon,
- heterocyclyl, aryl, ( $C_{1-6}$ )alkylamino or arylamino;

$R_5$  is optionally substituted

- saturated or unsaturated ( $C_{1-6}$ ) hydrocarbon or ( $C_{3-8}$ )cyclic hydrocarbon,
- heterocyclyl or aryl,

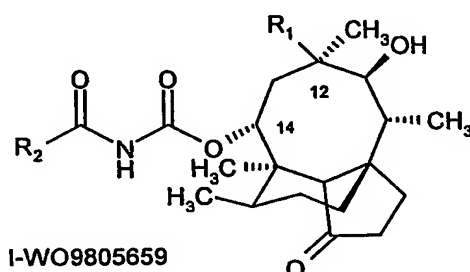
20  $R_6$  and  $R_7$  independently of each other are H, or optionally substituted

- saturated or unsaturated ( $C_{1-6}$ ) hydrocarbon or ( $C_{3-8}$ )cyclic hydrocarbon,

- heterocyclyl or aryl, or

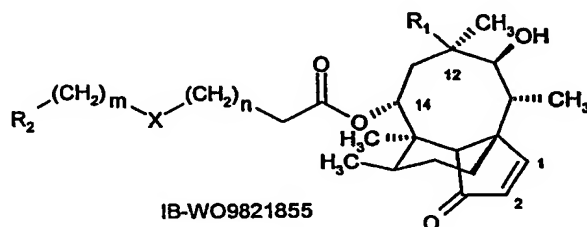
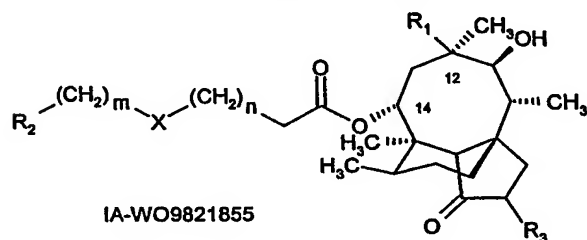
$R_6$  and  $R_7$  together with the nitrogen atom to which they are attached form an optionally substituted ( $C_{3-8}$ )cyclic group, optionally containing one additional heteroatom selected from N, O or S, and optionally fused to a hydrocarbon ring, a heterocyclic ring or an aromatic group;

- A compound as disclosed in WO9805659, e.g. of formula



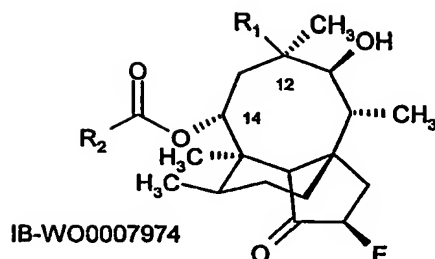
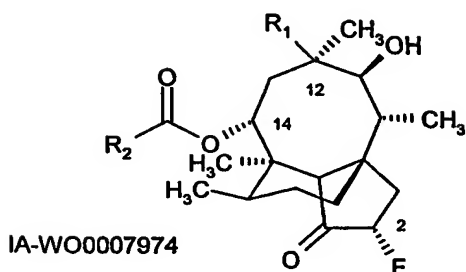
wherein  $R_1$  is vinyl or ethyl, and  $R_2$  is a group  $R_3$ ,  $R_4CH_2-$ , or  $R_5R_6CH=CH-$ , wherein ,  
each of  $R_3$  and  $R_4$  is an azabicyclic ring system, or  $R_5$  and  $R_6$  together with the carbon atom  
to which they are attached form an azabicyclic ring system;

- A compound of WO9821855; e.g. of formula



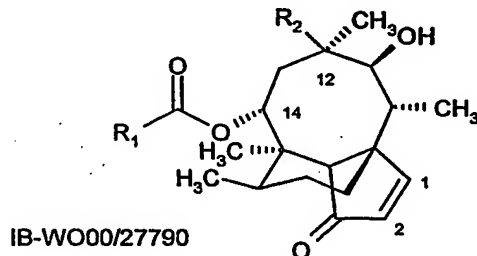
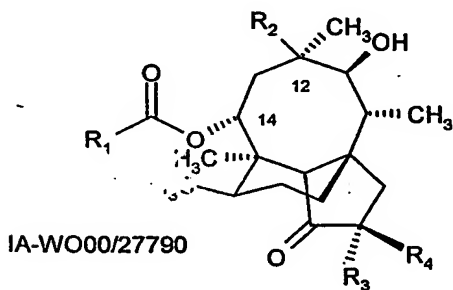
wherein  $n$  and  $m$  are independently of each other 0, 1 or 2;  $X$  is O, S, S(O),  $SO_2$ ,  $-COO-$ ,  
 $-NH-$ ,  $-CONH-$ ,  $-NHCONH-$ , or a bond;  $R_1$  is vinyl or ethyl;  $R_2$  is a non-aromatic monocyclic  
or bicyclic group containing one or two basic nitrogen atoms and attached through a ring  
carbon atom, e.g.  $R_2$  is optionally substituted quinuclidinyl, azabicyclo[2.2.1]heptyl,  
azabicyclo[4.3.0]nonyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.0]octyl, azabicyclo[2.2.2]octyl,  
azabicyclo[3.2.1]octenyl, azabicyclo[3.3.1]nonyl or azabicyclo[4.4.0]decyl;  $R_3$  is H, OH; or  
the moiety  $R_2(CH_2)_mX(CH_2)_nCH_2COO$  at position 14 of IA or IB is replaced by  
 $R_aR_bC=CHCOO$ , wherein one of  $R_a$  or  $R_b$  is hydrogen and the other is  $R_2$ ; or  $R_a$  and  $R_b$   
together form  $R_2$ ;

- A compound as disclosed in WO0007974, e.g. a 14-acyloxy derivative of mutilin or 19,20-  
dihydromutilin having a 2-fluoro substituent, such as of formula

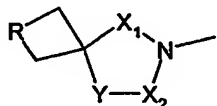


wherein  $R_1$  is vinyl or ethyl, and  $R_2\text{COO}^-$  is acyloxy, e.g.  $\text{HOCH}_2\text{CO}_2^-$  or  $\text{R-X-CH}_2\text{CO}_2^-$ , wherein  $X$  is  $\text{O}$ ,  $\text{S}$  or  $\text{NR}'$  and  $\text{R}$  and  $\text{R}'$  are independently of each other an aliphatic or aromatic group, preferably  $R_2\text{COO}^-$  is a carbamoyl group, such as a group  $\text{R}_3\text{R}_4\text{NCO}_2^-$  wherein  $\text{R}_3$  and  $\text{R}_4$  have various meanings (e.g.  $\text{R}_3$  and  $\text{R}_4$  have the meaning as disclosed for the meaning of  $\text{R}_2$  and  $\text{R}_3$  in WO9725309);

- A compound as disclosed in WO0027790, e.g. a compound of formula



wherein  $\text{R}_1$  is a  $\text{R}^{\text{A}}(\text{CH}_2)_n\text{O}(\text{CH}_2)_m$ ,  $\text{R}^{\text{A}}(\text{CH}_2)_p$ , or a group of formula

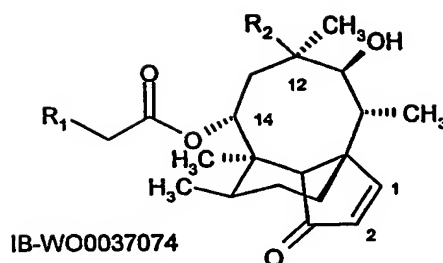
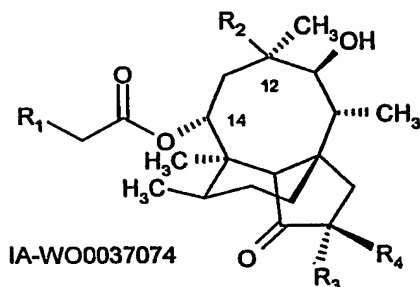


wherein  $\text{R}$  is a spiro-fused mono- or bicyclic ring containing one or two basic  $\text{N}$ -atoms;  $\text{X}_1$  and  $\text{X}_2$  which may be the same or different, are each  $-\text{CH}_2-$  or  $-\text{C}=\text{O}$ , provided that at least one of  $\text{X}_1$  and  $\text{X}_2$  is  $-\text{C}=\text{O}$ ; and  $\text{Y}$  is  $-\text{NH}-$ ,  $-\text{CH}_2-$  or  $-\text{CH}_2\text{-CH}_2-$ ;

$\text{R}^{\text{A}}$  is an optionally substituted aryl group or heteroaryl group linked via a carbon atom; e.g.  $\text{R}^{\text{A}}$  is optionally substituted phenyl, thienyl, pyridinyl, furyl, thiazolyl, isoxazolyl, benzimidazolyl, quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl or benzthiazolyl;

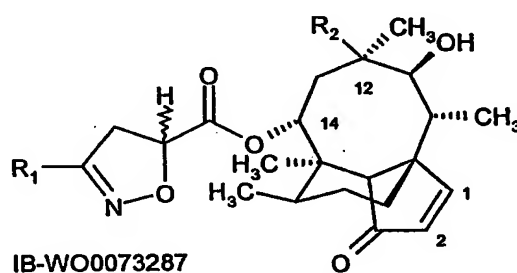
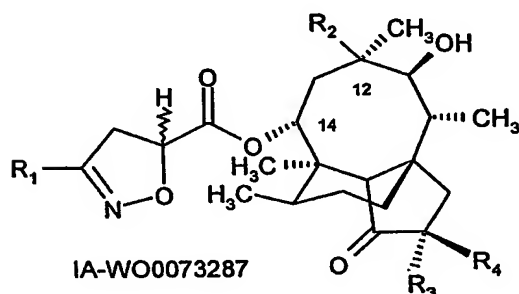
$m$  is 1, 2 or 3;  $n$  is 0, 1 or 2;  $p$  is 1 to 4;  $\text{R}_2$  is vinyl or ethyl; and  $\text{R}_3$  is  $\text{H}$ ,  $\text{OH}$  or  $\text{F}$ , and  $\text{R}_4$  is  $\text{H}$ ; or  $\text{R}_3$  is  $\text{H}$  and  $\text{R}_4$  is  $\text{F}$ ;

- A compound as disclosed in WO0037074, e.g. a compound of formula



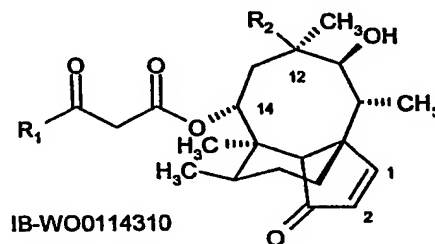
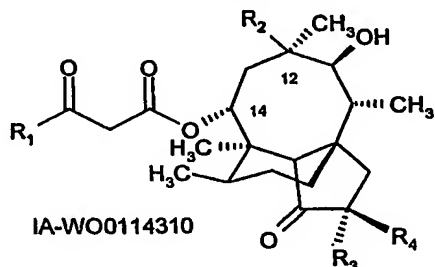
wherein  $R_1$  is an optionally substituted heteroaryl group which comprises a 5-membered heteroaromatic ring which has at least one N-atom, e.g. a pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, indole, benzimidazole, benzotriazole, 2-aza-indole or 6-aza-indole; and which is linked via a N-atom;  $R_2$  is vinyl or ethyl;  $R_3$  is H, OH or F, and  $R_4$  is H; or  $R_3$  is H and  $R_4$  is F;

- A compound as disclosed in WO0073287, e.g. a compound of formula



wherein  $R_1$  is optionally substituted aryl, e.g. azabicyclo-octyl; or an optionally substituted nitrogen containing ring, e.g. piperidinyl;  $R_2$  is vinyl or ethyl;  $R_3$  is H, OH or F and  $R_4$  is H; or  $R_3$  is H and  $R_4$  is F;

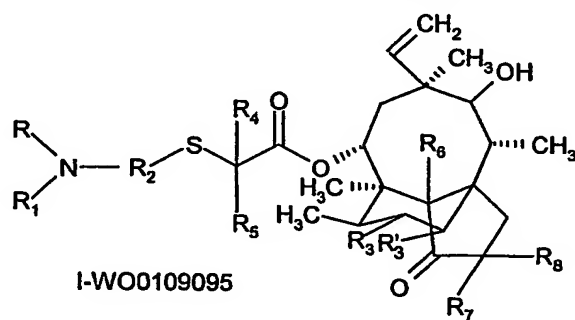
- A compound as disclosed in WO0114310, e.g. a compound of formula



wherein  $R_1$  is a nitrogen containing heterocycle, an optionally substituted aryl or optionally substituted heteroaryl, or  $CH_2R_5$ ,  
e.g.  $R_1$  is optionally substituted phenyl, 3-pyridyl, 4-pyridyl, pyrimidin-2-yl, 1,3,4-thiadiazol-2-yl, benzothiazol-2-yl, 2H-1,2,4-triazol-3-yl, azabicycloheptyl, azabicyclooctyl or piperidinyl;

$R_2$  is vinyl or ethyl;  $R_3$  is H, OH or F and  $R_4$  is H; or  $R_3$  is H and  $R_4$  is F;  $R_5$  is halogen or  $SR_6$ ; and  $R_6$  is aminoalkyl, a nitrogen containing heterocycle, or an optionally substituted aryl or optionally substituted heteroaryl; e.g.  $R_6$  is optionally substituted phenyl, 3-pyridyl, 4-pyridyl, pyrimidin-2-yl, 1,3,4-thiadiazol-2-yl, benzothiazol-2-yl, 2H-1,2,4-triazol-3-yl, azabicycloheptyl, azabicyclooctyl or piperidinyl;

- A compound as disclosed in WO0109095, e.g. a compound of formula



wherein R is hydrogen or alkyl;  $R_1$  is hydrogen or a group of formula

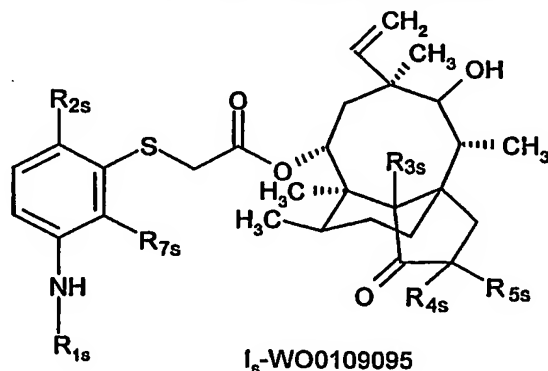


wherein X is S, O, or  $NR_{10}$ , wherein  $R_{10}$  is H or alkyl, or  $N^+(R'_{10})$ , wherein  $R'_{10}$  is alkyl

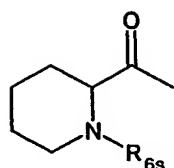
in the presence of an appropriate anion; and  $R_9$  is amino, alkyl, aryl, heterocyclyl or mercapto; and, if X is oxygen,  $R_9$  is additionally hydrogen;  $R_2$  is arylene, e.g. phenylene; or heterocyclene;  $R_4$  is hydrogen or alkyl;  $R_5$  is hydrogen or alkyl;  $R_3$ ,  $R_3'$ ,  $R_6$ ,  $R_7$  and  $R_8$  independently of each other are hydrogen or deuterium; or R and  $R_2$  together with the nitrogen atom to which they are attached form non-aromatic heterocyclene and  $R_1$  is a group of formula



wherein X and  $R_9$  are as defined above; e.g. a compound of formula



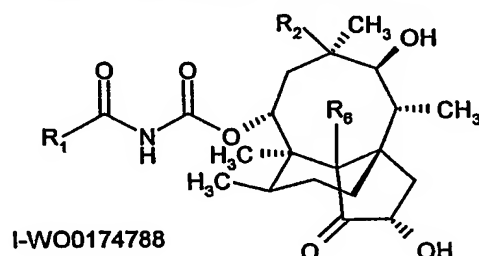
wherein  $R_{1s}$  is hydrogen or a group of formula



wherein  $R_{6s}$  is hydrogen or deuterium;  $R_{2s}$  is hydrogen, methyl or tert-butyl;

$R_{7s}$  is hydrogen or methyl; and  $R_{3s}$ ,  $R_{4s}$  and  $R_{5s}$  are hydrogen or deuterium;

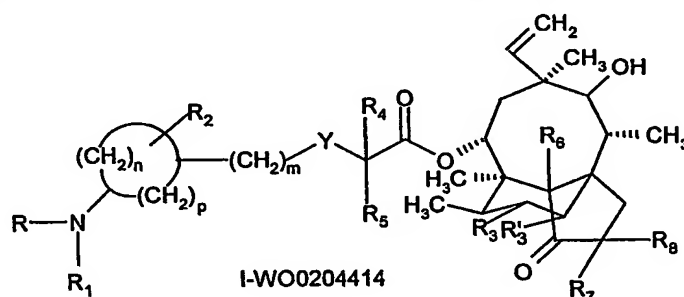
- A compound as disclosed in WO0174788, e.g. a compound of formula



- 5 wherein  $R_1$  is a 5- or 6-membered optionally substituted heteroaryl group;  
e.g. pyridine, pyridazine, pyrimidine, pyrazine, isoxazole, thiazole, imidazole, pyrazole,  
1,2,3-triazole, 1,2,4-triazole, benzimidazole, 3-oxo-3,4-dihydropyrido[2,3-b]pyrazine, or  
pyrazolo[1,5-a]pyrimidine; and  $R_2$  is vinyl or

- A compound as disclosed in WO0204414, e.g. a compound selected from 14-O-

- 10 [(cycloalkyl-sulfanyl)acetyl]mutilins; 14-O-[(cycloalkyl-alkyl-sulfanyl)acetyl] mutilins; 14-O-  
[(cycloalkoxy)acetyl]mutilins; or 14-O-[(cycloalkyl-alkoxy)acetyl] mutilins, such as of formula

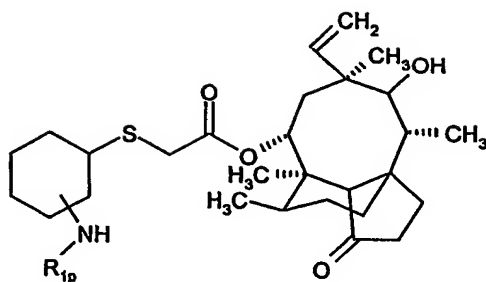


wherein R is hydrogen;  $R_1$  is hydrogen or a group of formula



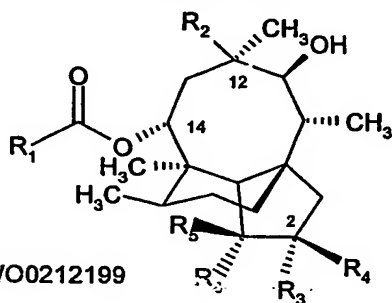
wherein X is sulphur, oxygen or  $\text{NR}_{10}$ , wherein  $R_{10}$  is hydrogen or alkyl; and  $R_9$  is

- 15 amino, alkyl, aryl or heterocyclyl; and, if X is oxygen,  $R_9$  is additionally hydrogen; Y is  
sulphur or oxygen;  $R_2$  is hydrogen or one or more substituents,  $R_4$  is hydrogen or alkyl;  $R_5$  is  
hydrogen or alkyl;  $R_3$  and  $R_{3'}$  are hydrogen, deuterium, or halogen;  $R_6$ ,  $R_7$  and  $R_8$  are  
hydrogen or deuterium; m is a number selected from 0 to 4; n is a number selected from 0  
to 10; and p is a number selected from 0 to 10; with the proviso that n plus p are at least 1;  
20 e.g. a compound of formula

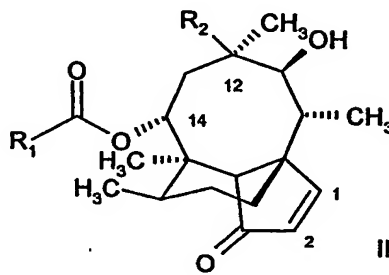
I<sub>p</sub>-WO0204414

wherein R<sub>1p</sub> is hydrogen or the residue of an amino acid;

- A compound as disclosed in WO0212199, e.g. a compound of formula



IA-WO0212199



IB-WO0212199

5 wherein R<sub>1</sub> is:

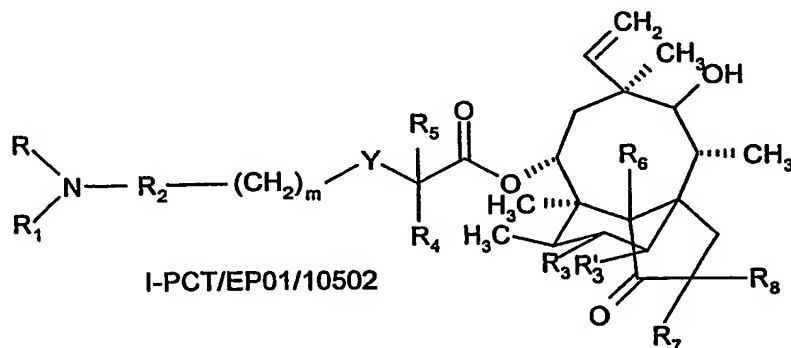
- a 5- or 6-membered aromatic or heteroaromatic ring attached via a ring carbon atom, preferably pyridyl, and comprising a substituent selected from halo, R<sub>7</sub>O-, R<sub>7</sub>S- or R<sub>8</sub>R<sub>9</sub>N- on a ring carbon adjacent to the carbon of attachment; or
- a 5- or 6-membered dihydro heteroaromatic ring attached via a ring carbon atom and comprising one oxygen or one or two nitrogen atoms and optionally fused to phenyl, a 5- or 6-membered heteroaryl ring comprising one or two nitrogen atoms or a 5- or 6-membered heterocyclyl ring comprising a sulphur, oxygen or nitrogen atom and further comprising a substituent selected from oxo or thioxo on a ring carbon adjacent to the carbon of attachment;
- a 6-membered tetrahydro heteroaromatic ring attached via a ring carbon atom comprising one or two nitrogen atoms and further comprising two substituents independently selected from oxo or thioxo wherein one of the substituents is on a ring carbon adjacent to the carbon of attachment; or
- a bicyclic heteroaryl ring attached via a ring carbon atom and comprising nine or ten ring atoms and from one to four nitrogen atoms;

wherein the ring of R<sub>1</sub> may be optionally further substituted; R<sub>2</sub> is vinyl or ethyl; R<sub>3</sub> is H, OH or F and R<sub>4</sub> is H, or R<sub>3</sub> is H and R<sub>4</sub> is F; and R<sub>5</sub> and R<sub>6</sub> together form an oxo group; or R<sub>3</sub>



and  $R_4$  is each H and  $R_5$  is H, or OH and  $R_6$  is H, or  $R_5$  is H and  $R_6$  is H or OH;  $R_7$  is optionally substituted ( $C_{1-6}$ )alkyl; and  $R_8$  and  $R_9$  are independently selected from hydrogen or optionally substituted ( $C_{1-6}$ )alkyl.

- A compound as disclosed in not yet published PCT-application PCT/EP01/10502, of formula

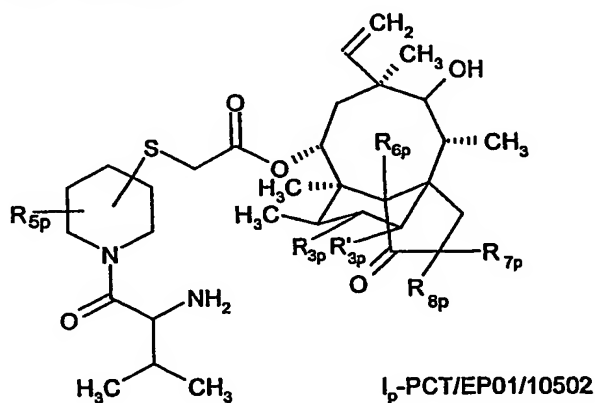


wherein  $R$  and  $R_2$  together with the nitrogen atom to which they are attached form pyrrolidiny or piperidiny,  $R_1$  is a group of formula



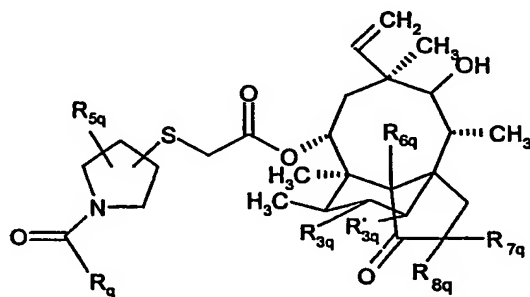
$R_3$  and  $R'_3$  are hydrogen, deuterium or halogen,  $R_4$  is hydrogen or alkyl,  $R_5$  is hydrogen or alkyl,  $R_6$ ,  $R_7$  and  $R_8$  are hydrogen or deuterium;  $R_9$  is amino, alkyl, aryl, heterocyclyl or mercapto; and, if  $X$  is oxygen,  $R_9$  is additionally hydrogen;  $R_{10}$  is hydrogen or alkyl,  $R'_{10}$  is alkyl,  $X$  is sulphur, oxygen,  $\text{NR}_{10}$ , or  $\text{N}^+(\text{R}'_{10})_2$  in the presence of an appropriate anion,  $Y$  is sulphur or oxygen, and  $m$  is 0, 1 or 2;

with the proviso that, when  $R$  and  $R_2$  together with the nitrogen atom to which they are attached form piperidiny,  $m$  is 0,  $Y$  is S and  $Y$  is attached in position 3 of said piperidine ring that group of formula I which is attached to the piperidine ring via the residue  $Y$  is either in the (S)-configuration or in the (R)-configuration, preferably in the (S)-configuration; preferably a compound of formula



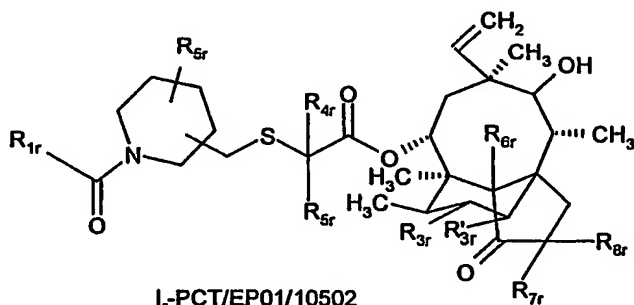
wherein  $R_{3p}$ ,  $R'_{3p}$ ,  $R_{6p}$ ,  $R_{7p}$  and  $R_{8p}$  are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for  $R_3$ ,  $R'_3$ ,  $R_6$ ,  $R_7$  and  $R_8$ ; and  $R_{5p}$  is hydrogen or one or more substituents, and if the group attached to the piperidine ring via the sulphur atom is in position 3 of said piperidine ring and  $R_{5p}$  is hydrogen, then the group attached to the sulphur atom is either in the (S)-configuration or in the (R)-configuration;

5 a compound of formula

I<sub>q</sub>-PCT/EP01/10502

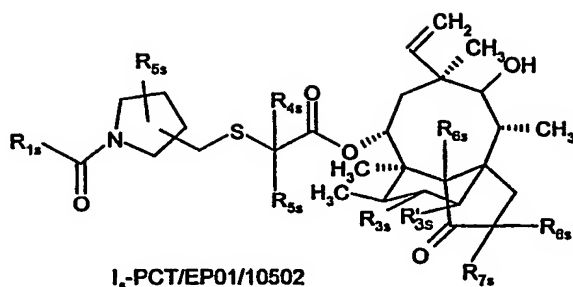
wherein  $R_{3q}$ ,  $R'_{3q}$ ,  $R_{6q}$ ,  $R_{7q}$  and  $R_{8q}$  are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for  $R_3$ ,  $R'_3$ ,  $R_6$ ,  $R_7$  and  $R_8$ ;  $R_{5q}$  is hydrogen or one or more substituents, preferably hydrogen; and  $R_q$  is that part of an amino acid which remains if the carboxylic group is splitted off;

10 a compound of formula

I<sub>r</sub>-PCT/EP01/10502

wherein  $R_{3r}$ ,  $R'_{3r}$ ,  $R_{4r}$ ,  $R_{6r}$ ,  $R_{7r}$  and  $R_{8r}$  are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for  $R_3$ ,  $R'_3$ ,  $R_4$ ,  $R_6$ ,  $R_7$  and  $R_8$ ;  $R_{5r}$  is hydrogen or one or more substituents, and  $R_{1r}$  is that part of an amino acid which remains if the carboxylic group is splitted off, or a compound of formula

15



wherein R<sub>3s</sub>, R'<sub>3s</sub>, R<sub>4s</sub>, R<sub>6s</sub>, R<sub>7s</sub> and R<sub>8s</sub>, respectively, are, index-number correspondingly, as defined for a compound of formula I-PCT/EP01/10502 for R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub>;

R<sub>5s</sub> is hydrogen or one or more substituents, preferably hydrogen; and R<sub>1s</sub> is that part of an amino acid which remains if the carboxylic group is splitted off; e.g. wherein in a compound of formula I<sub>s</sub> the group attached to the piperidine ring via the sulphur atom is either in the (S)-configuration or in the (R)-configuration; e.g. wherein in a group R<sub>1s</sub> the amine group of the amino acid residue is either in the (S)-configuration or in the (R)-configuration, such as the compounds

14-O-[(N-(3-Methyl-2-amino-buturyl-piperidin-3(S)-yl)sulfanyl)acetyl]mutilin, e.g. including 14-O-[(N-(3-Methyl-2(R)-amino-buturyl-piperidin-3(R)-yl)sulfanyl)acetyl]mutilin; and 14-O-[(N-(3-Methyl-2(S)-amino-buturyl-piperidin-3(S)-yl)sulfanyl)acetyl]mutilin;

14-O-[(N-(3-Methyl-2-amino-buturyl-piperidin-4-yl)sulfanyl)acetyl]mutilin, e.g. including 14-O-[(N-(3-Methyl-2(R)-amino-buturyl-piperidin-4-yl)sulfanyl)acetyl]mutilin, and

14-O-[(N-(3-Methyl-2(S)-amino-buturyl-piperidin-4-yl)sulfanyl)acetyl]mutilin; 14-O-[(N-(3-Methyl-2-amino-buturyl)-piperidin-3-yl)-methylsulfanylacetyl]-mutilin, e.g. including

14-O-[(N-(3-Methyl-2-amino-buturyl)-piperidine-3(S)-yl)-methylsulfanylacetyl]-mutilin, and 14-O-[(N-(3-Methyl-2-amino-buturyl)-piperidine-3(R)-yl)-methylsulfanylacetyl]-mutilin, such

as 14-O-[(N-(3-Methyl-2(S)-amino-buturyl)-piperidine-3(S)-yl)-methylsulfanylacetyl]-mutilin, and

14-O-[(N-(3-Methyl-2(R)-amino-buturyl)-piperidine-3(S)-yl)-methylsulfanylacetyl]-mutilin; 14-O-[(N-(3-Methyl-2-amino-buturyl)-pyrrolidine-2-yl)-methylsulfanylacetyl]-mutilin, e.g.

including 14-O-[(N-(3-Methyl-2-amino-buturyl)-pyrrolidine-2(R)-yl)-methylsulfanylacetyl]-mutilin, and 14-O-[(N-(3-Methyl-2-amino-buturyl)-pyrrolidine-2(S)-yl)-methylsulfanylacetyl]-mutilin, such as

14-O-[(N-(3-Methyl-2(R)-amino-butyl)-pyrrolidine-2(R)-yl)-methylsulfanylacetyl]-mutilin  
and

14-O-[(N-(3-Methyl-2(S)-amino-butyl)-pyrrolidine-2(R)-yl)-methylsulfanylacetyl]-mutilin,

14-O-[(N-(3-Methyl-2-amino-butyl)-pyrrolidin-3-yl)sulfanylacetyl]mutilin, e.g. including

5 14-O-[(N-(3-Methyl-2(R)-amino-butyl)-pyrrolidine-3-yl)-sulfanylacetyl]-mutilin and

14-O-[(N-(3-Methyl-2(S)-amino-butyl)-pyrrolidine-3-yl)-sulfanylacetyl]-mutilin;

and

14-O-[(N-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin, e.g. including

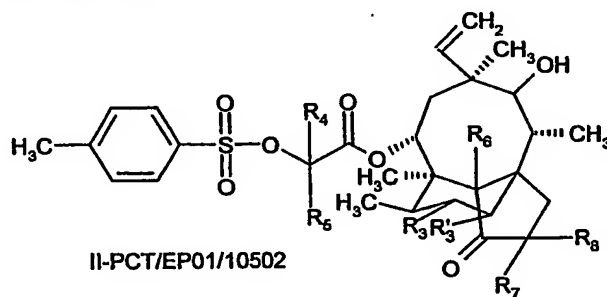
4-O-[(N-(R)-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin, and

10 4-O-[(N-(S)-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin.

e.g. in free form or in the form of a salt, e.g. a salt with hydrochloric acid; such as a  
hydrochloride.

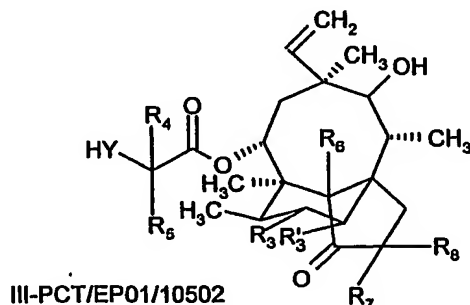
14-O-[(N-histidinyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin is 14-O-[(N-(3-(imidazol-4yl)-2-  
amino-propionyl-pyrrolidin-3-yl)sulfanylacetyl]mutilin.

15 A compound of formula PCT/EP01/10502 may be obtained as appropriate, e.g. according,  
e.g. analogously, to a method as conventional, e.g. by a process comprising the steps  
a. reacting a compound of formula



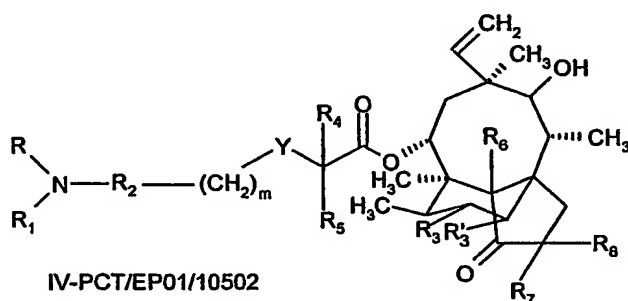
wherein R<sub>3</sub>, R'<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined in claim 1 of PCT/EP01/10502 and R<sub>6</sub>, R<sub>7</sub> and

20 R<sub>8</sub> are hydrogen, with urea or thiourea and subsequent reduction to obtain a compound of  
formula



wherein Y is as defined in claim 1 of PCT/EP01/10502;  $R_3$ ,  $R'_3$ ,  $R_4$  and  $R_5$  are as defined above and  $R_6$ ,  $R_7$  and  $R_8$  are hydrogen,

- b. reacting a compound of formula III as defined in step a. with optionally substituted pyrrolidine, methyl or ethyl pyrrolidine, piperidine, methyl or ethyl piperidine (= methyl-, ethyl- pyrrolidine or piperidine), respectively, carrying at the nitrogen atom a group of formula  $-C(=X)R_9$ , wherein X and  $R_9$  are as defined in claim 1 of PCT/EP01/10502, in the form of a reactive derivative, e.g. in the form of a mesylate or a tosylate; to obtain a compound of formula

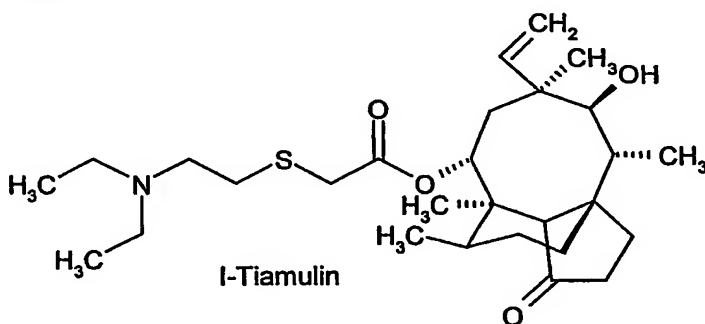


which is a compound of formula I of PCT/EP01/10502 wherein  $R$ ,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R'_3$ ,  $R_4$ ,  $R_5$ , Y and m are as defined in claim 1 of PCT/EP01/10502 and  $R_6$ ,  $R_7$  and  $R_8$  are hydrogen; and, if desired,

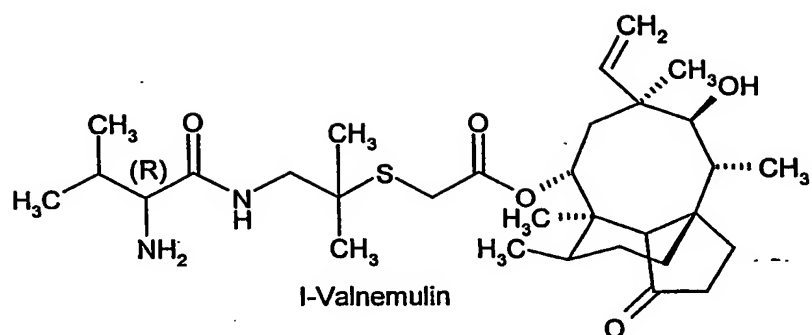
- c. introducing deuterium into a compound of formula IV as defined in step b, to obtain a compound of formula I, wherein  $R$ ,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R'_3$ ,  $R_4$ ,  $R_5$ , Y and m are as defined above and  $R_6$ ,  $R_7$  and  $R_8$  are deuterium.

A pleuromutilin of the present invention is preferably a compound of formula US4278674, a compound of formula EP0153277, a compound of formula WO0109095, a compound of formula WO0204414 or a compound of formula PCT/EP01/10502, e.g. including

- a compound of formula

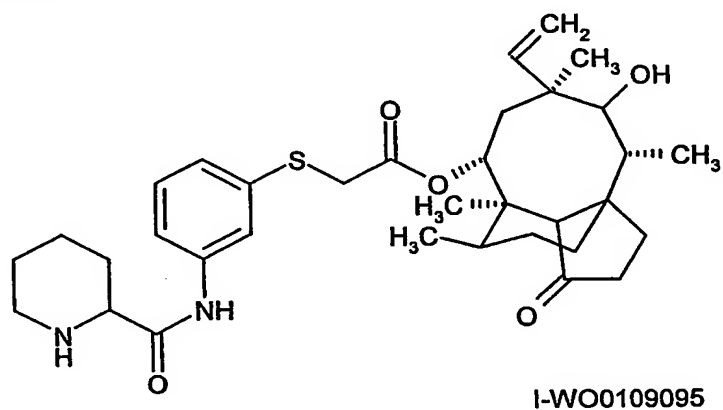


- a compound of formula



e.g. in the form of a hydrochloride;

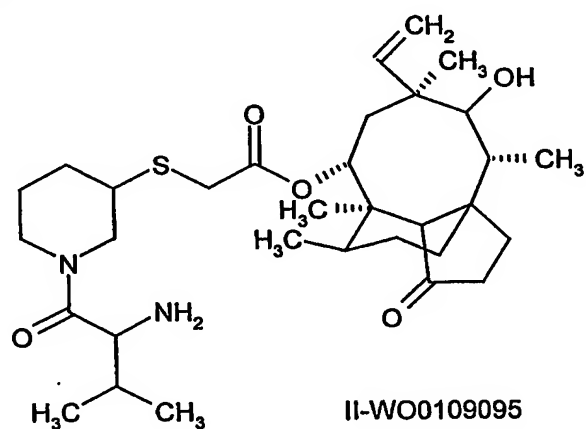
- a compound of formula



**I-WO0109095**

5 e.g. in the form of a hydrochloride;

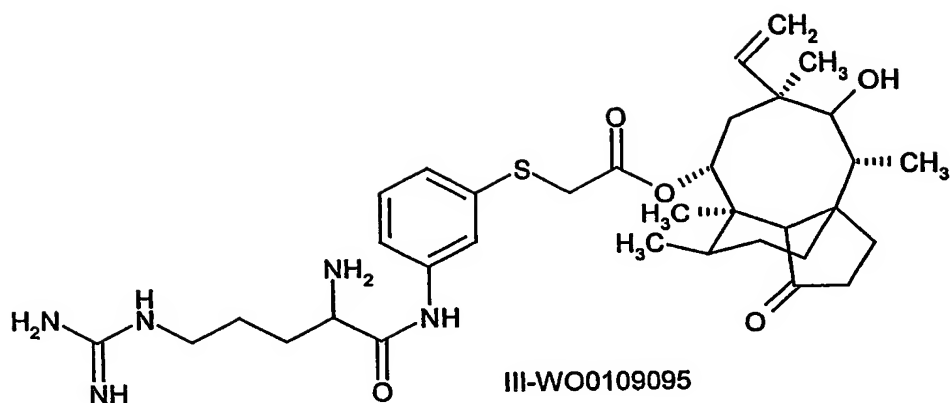
- a compound of formula



II-WO0109095

e.g. in the form of a hydrochloride; and

- a compound of formula



e.g. in the form of a hydrochloride.

Activity against strains of *Mycobacterium*, e.g. *M.tuberculosis* may be determined according to the following General Test Procedure:

#### General Test procedure

Is carried out according to the known and appropriate Agar Dilution Test.

Agar is used as a substrate. Shortly before solidification of the Agar TEST COMPOUNDS in different concentrations are added and mixed into the still liquid agar mass (according to the Agar dilution test). Controls without TEST COMPOUNDS are also prepared for determination of strain growth ability. The thus prepared agars are inoculated after solidification with *Mycobacterium tuberculosis* strains. Incubation is carried out in normal incubators at 37°C. As a nutrition medium Middlebrook 7H10 + OADC (Oleic, Albumin, Dextrose, Catalase) Enrichment (pH 6.71- 6.73) is used.

The minimum inhibition concentration (MIC) which is the compound concentration in the agar which inhibits 99% of strain growth, is determined after 3 weeks, 4 weeks and 5 weeks after inoculation.

Pleuromutilins of the present invention show activity against strains of *Mycobacterium*, e.g. *M.tuberculosis* and are thus useful in the treatment of infections caused by *Mycobacterium*. Pleuromutilins of the present invention surprisingly are even active against resistant and multiresistant *M.tuberculosis* strains, e.g. strains which are resistant against treatment with known pharmaceuticals useful in the treatment of tuberculosis, e.g. Isoniacid, Rifampicin, Streptomycin.

**Example 1****Determination of *Mycobacterium tuberculosis* strain resistance**

Activity of the known compounds Isoniacid, Rifampicin and Streptomycin against *M.tuberculosis* strains 1 to 14 as set out in TABLE 1 is determined in the Agar Dilution Test according to the method as described in the General Procedure. The MIC is determined after 3, 4 and 5 weeks. The strains 1 to 7 tested were found to be either sensible (S) or resistant (R) against Isoniacid, Rifampicin and/or Streptomycin. Results are as set out in TABLE 1 below:

TABLE 1

<i>M.tuberculosis</i>	Isoniacid	Rifampicin	Streptomycin
Strain 1	S	S	S
Strain 2	S	S	S
Strain 3	R	R	S
Strain 4	R	R	R
Strain 5	R	R	S
Strain 6	S	S	S
Strain 7	R	S	R
Strain 8	S	R	S
Strain 9	R	S	R
Strain 10	S	S	S
Strain 11	S	S	S
Strain 12	S	S	S
Strain 13	S	S	S
Strain 14	S	S	S
Strain 15	S	S	S

Strain 15 is the labor strain 137kV. Resistant and sensible strains are isolated from patients with known sensibilities/resistance. A strain is designated as resistant if its MIC in testing according to the General Test Procedure after 3 to 5 weeks is higher than 20 µg/ml.

**Example 2**

Activity of TEST COMPOUNDS (TCs) against *M.tuberculosis* strains 1 to 5 and 7 as set out in TABLE 1 is determined in the Agar Dilution Test under conditions as in Example 1 in different agar concentrations of the TEST COMPOUNDS.



The MIC is determined after 3, 4 and 5 weeks.

Activity of the following TEST COMPOUNDS (TC) is tested:

- A compound of formula I-Tiamulin: TC-1
- 5 A compound of formula I-Valnemulin: TC-2
- A compound of formula I-WO0109095: TC-3
- A compound of formula II-WO0109095: TC-4
- A compound of formula III-WO0109095: TC-5
- 10 Test results are as set out in TABLE 2 below are obtained:

TABLE 2

TC/week	MIC ( $\mu\text{g/ml}$ ) against <i>Mycobacterium tuberculosis</i> of strain number					
	1	2	3	4	6	7
TC-1/3	5	5	5	5	10	10
TC-1/4	5	5	5	10	10	20
TC-1/5	5	5	5	10	10	20
TC-2/3	0.5	1	1	5	5	5
TC-2/4	0.5	5	1	5	5	5
TC-2/5	0.5	5	5	5	5	10
TC-3/3	1	5	5	1	5	20
TC-3/4	1	5	5	5	10	20
TC-3/5	1	5	5	10	10	20
TC-4/3	0.5	5	1	1	5	5
TC-4/4	1	5	1	5	5	5
TC-4/5	1	5	5	5	5	5
TC-5/3	1	5	5	5	5	5
TC-5/4	5	5	5	5	10	10
TC-5/5	5	5	5	10	10	10

### Example 3

- 15 Is carried out according to the method of example 2. Test results obtained are as set out in TABLE 3 and in TABLE 4:

TABLE 3

TC/week	MIC (µg/ml) against <i>Mycobacterium tuberculosis</i> of strain number							
	1	2	3	4	5	6	7	8
TC-2/3	0.5	4	2	8	2	4	4	4
TC-2/4*)	0.5	4	2	8	4	4	8	8
TC-4/3	1	4	1	4	2	4	2	2
TC-4/4	2	4	1	4	2	4	4	2
TC-4/5	2	4	1	4	2	4	4	4

\*) Tested after 31 days and thus no further testing after 5 weeks.

TABLE 4

TC/week	MIC (µg/ml) against <i>Mycobacterium tuberculosis</i> of strain number					
	10	11	12	13	14	15
TC-2/3	4	2	4	4	4	2
TC-2/4*)	4	4	4	8	4	4
TC-4/3	2	2	2	2	4	2
TC-4/4	2	2	2	2	4	2
TC-4/5	4	2	4	4	4	4

5 \*) Tested after 31 days and thus no further testing after 5 weeks.

10 In TABLES 2 to 4 in the column "TC/week" the term "TC-number" indicates the TEST COMPOUND as defined above, e.g. TC-1 indicates a compound of formula I-Tiamulin; and "/week" indicates the MIC-determination point (in weeks from inoculation) in the testing of such TEST COMPOUND. "TC-1/3" for example indicates that the MIC of a compound of formula I-Tiamulin was determined after 3 weeks from inoculation.

15 MIC is the minimum inhibition concentration as defined above. The strain numbers 1 to 4 and 6 to 7 indicated in TABLE 2, the strain numbers 1 to 9 indicated in TABLE 3 and the strain numbers 10 to 15 indicated in TABLE 4 refer to the corresponding *Mycobacterium tuberculosis* strains of example 1.

# Patent Claims

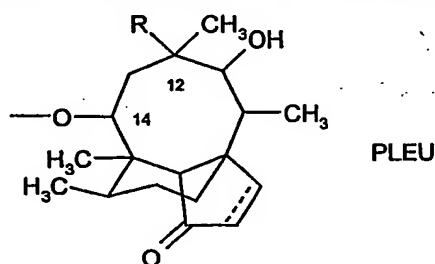
1. Use of a pleuromutilin in the preparation of a medicament for the treatment of diseases caused by *Mycobacterium*.

5

2. A method of preventing or treating diseases caused by *Mycobacterium*, comprising administering to a subject in need of such treatment an effective amount of a pleuromutilin.

- 10 3. Use according to claim 1 or a method according to claim 2 wherein *Mycobacterium* is *Mycobacterium tuberculosis*.

4. Use or a method according to any one of the preceding claims wherein a pleuromutilin is a compound comprising the basic structural elements as set out in formula

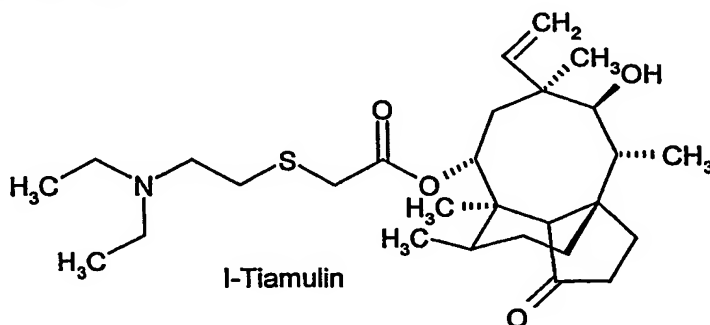


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wherein R is vinyl or ethyl and the dotted line is a bond or is no bond.

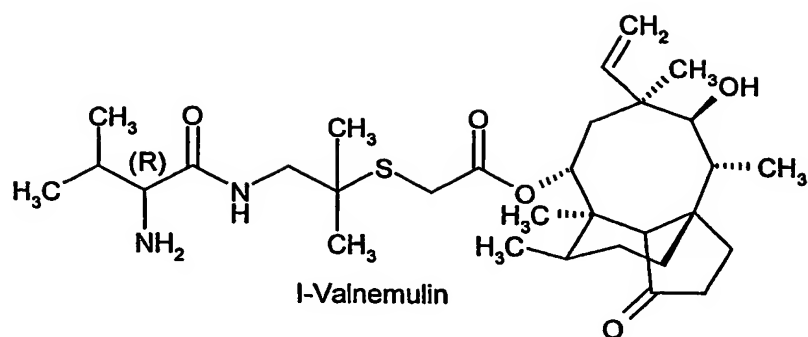
5. Use or a method according to claim 4 wherein a pleuromutilin is selected from the group consisting of

- 20 - a compound of formula

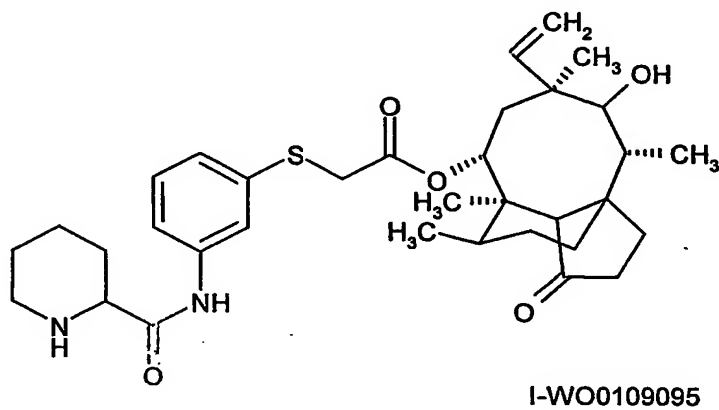


- a compound of formula

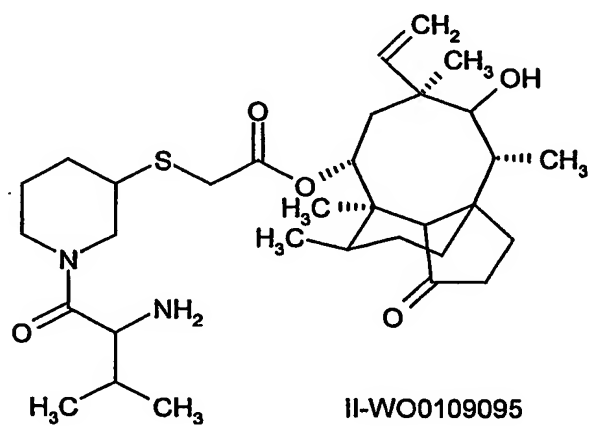
- 25 -



- a compound of formula



a compound of formula

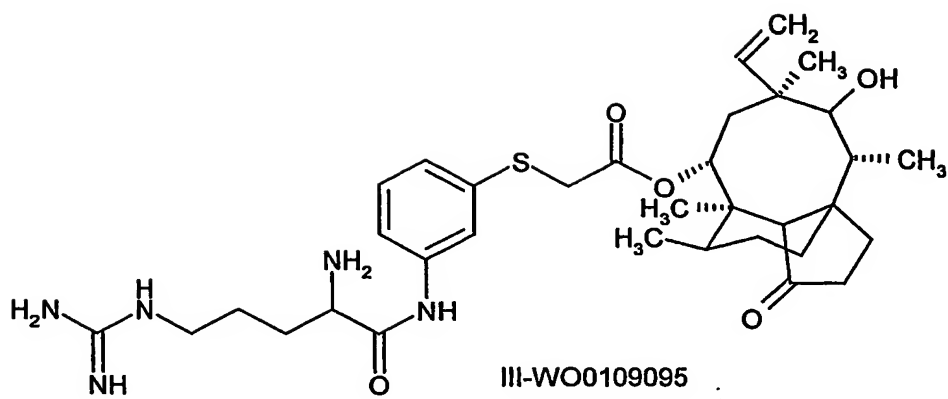


5

and

- a compound of formula

- 26 -



SC/27-Mar-02

**Abstract**

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A method of preventing or treating diseases caused by *Mycobacterium*, comprising administering to a subject in need of such treatment an effective amount of a pleuromutilin.

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